(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 379 147**
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 90100841.7

(51) Int. Cl.5: A61K 47/36

(22) Date of filing: 16.01.90

Claims for the following Contracting State: GR.

(30) Priority: 17.01.89 US 297720
27.11.89 US 441849

(43) Date of publication of application:
25.07.90 Bulletin 90/30

(84) Designated Contracting States:
BE CH DE DK FR GB GR IT LI NL SE

(71) Applicant: STERLING DRUG INC.
90 Park Avenue
New York New York(US)

(72) Inventor: Gorman, William George
25 Old Troy Road
East Greenbush, New York, 12061(US)
Inventor: Mariani, Elio Paul
34 Cloverfield Drive
Loudonville, New York, 12211(US)

(74) Representative: Baillie, Iain Cameron et al
c/o Ladas & Parry Isartorplatz 5
D-8000 München 2(DE)

(54) Extrudable elastic gel for use as carrier for therapeutic agent.

(57) An extrudable elastic oral pharmaceutical gel composition being a solution and consisting essentially of by weight/volume from about 0.1% to about 50% of a therapeutically active agent or a mixture of two or more therapeutically active agents, from about 5% to about 40% of an alcoholic solvent which is ethanol, propylene glycol, glycerin or polyethylene glycol having the structural formula $H-(OCH_2CH_2)_n-OH$ wherein n is an integer from 4 to 180 or a mixture thereof, from about 5% to about 40% of a hexitol which is sorbitol, mannitol or hydrogenated maltose syrup or a mixture thereof, from about 25% to about 85% of water, and from about 0.2% to about 5% of a seaweed polysaccharide which is agar, algin, carrageenan or furcelleran or a mixture thereof.

EP 0 379 147 A2

The invention relates to extrudable elastic oral pharmaceutical gel compositions and metered dose dispensers containing them and method of making and method of use thereof.

U.S. Pat. 4,708,834 issued Nov. 24, 1987 describes pharmaceutical gel compositions as fills for gelatin capsules. The fill compositions are described as "comprising an aqueous solution or dispersion of a polysaccharide gum and a pharmaceutically-active compound". Most of the water thereof is described as being removed after encapsulation by drying the capsules. Acetaminophen and niacin fill compositions and capsules are specifically described.

There is a need for oral pharmaceutical compositions for pediatric and adult/geriatric use in an easy to use metered dose form. An attempt to fill this need is shown by U.S. Pat. 4,639,367 which describes "stable, edible anhydrous aerosol foam[s] or whip[s] capable of suspending up to 50% by weight of a dispersed solid...prepared from a foamable, edible anhydrous liquid oil; a foaming agent; and controlled amounts of a food grade propellant which are sufficient to produce a stable foam rather than a spray". Such products appear to be illustrated by Extra Strength MAALOX® WHIP ™ Antacid brand of magnesium and aluminum hydroxides oral suspension, which is described by Physicians' Desk Reference for Nonprescription Drugs (ninth edition 1988, pp. 423 and 667). These compositions suffer the disadvantages of high caloric content due to the edible oil, potential for gastric and intestinal distress due to the aerosol propellant, inexact metering and tendency for the aerosol dispenser nozzle to clog due to the particulate nature of the compositions.

The present invention relates an extrudable elastic oral pharmaceutical gel composition which is a solution and consisting essentially of by weight/volume from about 0.1% to about 50% of a therapeutically active agent or a mixture of two or more therapeutically active agents, from about 5% to about 40% of an alcoholic solvent which is ethanol, propylene glycol, glycerin or polyethylene glycol having the structural formula $H\text{-}(OCH_2CH_2)_n\text{-}OH$ wherein n is an integer from 4 to 180 or a mixture thereof, from about 5% to about 40% of a hexitol which is sorbitol, mannitol or hydrogenated maltose syrup or a mixture thereof, from about 25% to about 85% of water, and from about 0.2% to about 5% of a seaweed polysaccharide which is agar, algin, carrageenan or fucelleran or a mixture thereof.

The above-described extrudable elastic oral pharmaceutical gel composition may be contained within a manually operable dispenser capable of delivering a metered dose of the composition as an extrudate. The above-described extrudable elastic oral pharmaceutical gel composition is prepared by mixing the ingredients thereof and then, if desired, filling an above-described manually operable dispenser therewith. One can then dispense a metered dose of an above-described extrudable elastic oral pharmaceutical gel composition from an above-described manually operable dispenser.

The therapeutically active agent can be any medicinal compound which is soluble in the composition, stable on admixture with the other ingredients of the composition and effective on oral administration of the composition or a combination of any two or more such compounds and is preferably an analgesic, antihistamine, antitussive, expectorant, or oral nasal decongestant. The analgesic is preferably acetaminophen or ibuprofen. The antihistamine is preferably brompheniramine maleate, chlorpheniramine maleate, doxylamine succinate, phenidamine tartrate and pyrilamine maleate. The antitussive is preferably selected from the group consisting of codeine or a pharmaceutically acceptable acid addition salt thereof, dextromethorphan or a pharmaceutically acceptable acid addition salt thereof and diphenhydramine hydrochloride. The expectorant is preferably selected from the group consisting of guaifenesin and potassium guaicacolsulfonate. The oral nasal decongestant is preferably selected from the group consisting of phenylephrine or a pharmaceutically acceptable acid addition salt thereof, phenylpropanolamine or a pharmaceutically acceptable acid addition salt thereof and pseudoephedrine or a pharmaceutically acceptable acid addition salt thereof.

The polyethylene glycols having the structural formula $H\text{-}(OCH_2CH_2)_n\text{-}OH$ wherein n is an integer from 4 to 180 have molecular weights in the range from 194 to 7948, respectively, and can also be defined thereby, that is, as having molecular weights in the range from about 200 to about 8000. A mixture of two or more such polyethylene glycols can also be used. The names thereof used herein are the CTFA (The Cosmetic, Toiletry and Fragrance Association, Inc., 1110 Vermont Avenue, N.W., Washington, D.C. 20005) Adopted Names as defined in the CTFA Cosmetic Ingredient Dictionary (Third Edition, 1982) and supplements thereof. The names given therein for the polyethylene glycols all begin with a acronym PEG and range from PEG-4 (the first entry) to PEG-90M (the last entry). PEG-4 defines the polyethylene glycol of the foregoing structural formula wherein "n has an average value of 4". Since the polyethylene glycols are synthetic polymers, the value of n is not the same for every molecule of a sample and is therefore expressed as an average. In PEG-90M "n has an average value of 90000". PEG-6-32 is defined as a mixture of PEG-6 wherein n has an average value of 6 and PEG-32 wherein n has an average value of 32. Accordingly the CTFA Adopted Names of the polyethylene glycols reflect the molecular structures thereof.

Hydrogenated maltose syrup is defined as the substance made by hydrogenation of special high maltose syrup obtained from enzymatic hydrolsis of food starch. The substance contains a significant amount of sorbitol. LYCASIN® of hydrogenated maltose syrup is sold by Roquette Corporation.

The seaweed polysaccharides are described generally and specifically in a book entitled "Industrial Gums" (subtitle, "Polysaccharides and Their Derivatives", Second Edition: Roy L. Whistler, editor; James N. BeMiller, assistant editor; Academic Press, New York and London, 1973), wherein they are also referred to as seaweed extracts (heading of chapters III-IX) and seaweed gums (chapter I by Roy L. Whistler, page 8). A separate chapter among chapters III-IX is devoted to each of agar (chapter III by H.H. Selby and W.H. Wynne), algin (chapter IV by William H. McNeely and David J. Pettitt), carrageenan (chapter V by Gordon A. Towle) and furcelleran (chapter VII by E. Bjerre-Petersen, J. Christensen and P. Hemmingsen). Each of these substances is also described by a monograph of the Merck Index (Tenth Edition, 1983): agar by monograph 169, algin by monograph 228 (monograph 229 describes alginic acid), carrageenan by monograph 1848 and furcelleran by monograph 4177.

The concentration of therapeutically active agent in the composition is determined by the effective dose of the therapeutically active agent, the amount of composition to be delivered in a single dose and the number of doses to be administered in a given period of time. A typical single dose of composition is about 2.5 ml. If for example the effective dose of therapeutically active agent is 100 mg. and the dose is 2.5 ml., the concentration of therapeutically active agent is 4% by weight/volume. Table I shows the range of effective daily doses of each of the above-named preferred therapeutically active agents whereby the concentration thereof, depending on the number of doses to be administered per day, is determined. .

Table I

Effective Daily Doses of Therapeutically Active Agents	
Therapeutically Active Agent	Range of Effective Daily Dose (mg.)
Acetaminophen	800-4000
Ibuprofen	200-1200
Brompheniramine Maleate	6-24
Chlorpheniramine Maleate	6-24
Doxylamine Succinate	18.75-75
Phenindamine Tartrate	37.5-150
Pyrilamine Maleate	50-200
Codeine	30-120
Dextromethorphan	30-120
Diphenhydramine Hydrochloride	37.5-150
Guaifenesin	600-2400
Potassium Guaiacolsulfonate	75-300
Phenylephrine	15-60
Phenylpropanolamine	37.5-150
Pseudoephridine	60-240

In addition to the essential ingredients the composition can contain one or more pharmaceutical adjuncts, which can include preservatives, dyes and flavors.

The compositions of the invention are generally prepared by gently mixing the ingredients at a temperature in the range of 0-100° C., preferably 20- 70° C. When the solubility of the therapeutically active agent in water is low, it is first dissolved in the alcoholic solvent or solvent mixture. So as not to precipitate it the water is added slowly and carefully. The seaweed polysaccharide can be added at any stage of the mixing but is preferably added last to avoid gelling during the mixing. Vigorous mixing is avoided to minimize entrapment of air bubbles in the composition upon gelling. The following composition of the invention containing acetaminophen as the therapeutically active agent was prepared.

EXAMPLE	
Ingredient	% Weight/Volume
Acetaminophen, USP	3.20x
PEG-6-32	20.0xx
Propylene Glycol	5.00x
Glycerin	5.00x
Sorbitol Solution, 70%	40.0xx
Potassium Sorbate	0.300
Benzoic Acid	0.100
FD & C Red # 40 Dye	0.010
Cherry/Raspberry Flavor	0.094
Calcium Saccharin	0.180
Carrageenan	1.50x
Purified Water to make	100.0xx

In this composition the potassium sorbate and benzoic acid are preservatives. The PEG-6-32, propylene glycol, glycerin, sorbitol solution and about 90% of the purified water were placed into a manufacturing kettle and warmed to about 45° C. with gentle mixing. The acetaminophen, potassium sorbate, benzoic acid and calcium saccharin were added with further mixing. The mixture was cooled to room temperature and the dye and flavor were added with further mixing. The remainder of the purified water was added with further mixing. The preferred pH is 4.5 and can be adjusted at this stage if necessary with hydrochloric acid or sodium hydroxide. The mixture was warmed to 65° C. and the carrageenan was added with further mixing until dissolved. The resulting mixture, which was a solution was poured into a manually operable dispenser capable of delivering a metered dose of the composition as an extrudate and allowed to cool. The dispenser dispensed a metered dose of about 2 ml. containing about 64 mg. of acetaminophen.

The compositions of the invention including that of the foregoing example are elastic, that is they coalesce if separated. They are not rigid or rubbery but are soft and can be extruded. They are formulated to be taken by mouth. A dose thereof can be measured out by weight or volume manually and administered directly, for example, by spoon from a jar, but the preferred means of administration is by metered dose from a manually operable dispenser similar to the type presently used for dispensing toothpastes and generally disclosed in U.S. Pat. 4,511,068 and U.S. Pat. 4,685,593. The metered dose can be dispensed into a spoon, then taken orally, thus avoiding manually measuring out the dose and thus providing a convenient dosage form for the very young, the very old and even those in between.

A preferred manually operable dispenser is sold by Calmar Inc. (40 Stirling Road, Watchung, NJ 07060) under the name High Viscosity Dispenser (HVD) and is described by two brochures, one entitled Product Dispenser News and the other entitled FACT SHEET. The latter cites U.S. Pat. 4,511,608.

Another preferred manually operable dispenser is sold by The English Glass Company Limited (Scudamore Road, Leicester LE31UG, England) under the name VARIO Dispenser and is described by a brochure entitled THE NEW VARIO DISPENSER FROM englass®.

A preferred combined manufacture and composition of matter aspect of the invention is the acetaminophen gel composition of the foregoing example contained within the HVD or VARIO Dispenser.

A preferred first process aspect of the invention is the method of making the preferred combined manufacture and composition of matter aspect of the invention which comprises first preparing the acetaminophen gel composition of the foregoing example by mixing the ingredients thereof and then filling the HVD or VARIO Dispenser therewith.

A preferred second process aspect of the invention is the method of using the preferred combined manufacture and composition of matter aspect of the invention which comprises dispensing a metered dose of the acetaminophen gel composition of the foregoing example from the HVD or VARIO Dispenser.

Claims

1. An extrudable elastic oral pharmaceutical gel composition being a solution and consisting essentially of by weight/volume from about 0.1% to about 50% of a therapeutically active agent or a mixture of two or more therapeutically active agents, from about 5% to about 40% of an alcoholic solvent which is ethanol,

propylene glycol, glycerin or polyethylene glycol having the structural formula H-(OCH_2CH_2)$_n$-OH wherein n is an integer from 4 to 180 or a mixture thereof, from about 5% to about 40% of a hexitol which is sorbitol, mannitol or hydrogenated maltose syrup or a mixture thereof, from about 25% to about 85% of water, and from about 0.2% to about 5% of a seaweed polysaccharide which is agar, algin, carrageenan or furcelleran or a mixture thereof.

2. A composition according to claim 1, wherein the therapeutically active agent is an analgesic, antihistamine, antitussive, expectorant or oral nasal decongestant.

3. A composition according to claim 2, wherein the therapeutically active agent is acetaminophen, ibuprofen, brompheniramine maleate, chlorpheniramine maleate, doxylamine succinate, phenidamine tartrate, pyrilamine maleate, codeine, dextromethorphan, diphenhydramine hydrochloride, guaifensin, potassium guaiacolsulfonate, phenylephrine, phenylpropanolamine or pseudoephridine.

4. A composition according to claim 3, wherein the therapeutically active agent is acetaminophen.

5. A composition according to claim 4, wherein the alcoholic solvent is a mixture of propylene glycol, glycerin and polyethylene glycol and wherein the polyethylene glycol is a mixture of the polyethylene glycol wherein n is 6 and the polyethylene glycol wherein n is 32.

6. A composition according to claim 5, wherein the hexitol is sorbitol.

7. A composition according to claim 6, wherein the seaweed polysaccharide is carrageenan.

8. A composition according to claim 7, consisting essentially of by weight/volume about 3.2% acetaminophen, about 5% propylene glycol, about 5% glycerin, about 28% sorbitol, about 20% of the polyethylene glycol mixture, about 1.5% carrageenan and about 36.6% water.

9. A composition according to any one of the preceding claims, which is contained within a manually operable dispenser capable of delivering a metered dose of the composition as an extrudate.

10. A composition according to claim 9, wherein the metered dose has a volume of about 2 ml. containing about 64 mg. of acetaminophen.

Claims for the following contracting State: GR

1. A carrier for a therapeutic agent comprising an extrudable elastic oral pharmaceutical gel composition which consists essentially of by weight/volume from about 5% to about 40% of an alcoholic solvent which is ethanol, propylene glycol, glycerin or polyethylene glycol having the structural formula H-(OCH_2CH_2)$_n$-OH wherein n is an integer from 4 to 180 or a mixture thereof, from about 5% to about 40% of a hexitol which is sorbitol, mannitol or hydrogenated maltose syrup or a mixture thereof, from about 25% to about 85% of water, and from about 0.2% to about 5% of a seaweed polysaccharide which is agar, algin, carrageenan or furcelleran or a mixture thereof, on the basis of the total weight of said carrier and the therapeutic agent with which it is to be admixed.

2. A carrier according to claim 1, wherein the alcoholic solvent is a mixture of propylene glycol, glycerin and polyethylene glycol and wherein the polyethylene glycol is a mixture of the polyethylene glycol wherein n is 6 and the polyethylene glycol wherein n is 32.

3. A carrier according to claim 2, wherein the hexitol is sorbitol.

4. A carrier according to claim 3, wherein the seaweed polysaccharide is carrageenan.

5. A carrier according to claim 4, consisting essentially of by weight/volume about 3.2% acetaminophen, about 5% propylene glycol, about 5% glycerin, about 28% sorbitol, about 20% of the polyethylene glycol mixture, about 1.5% carrageenan and about 36.6% water.